McGill Copy.

cc: Drs. Little
Wilson

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July 23, 1951

MEMORANDUM

TO: The Subcommittee on Project #174 (Strong and McGill).
Drs. Cattell, Bing and Lynch.

FROM: Robert C. Hockett

An application for continued support has reached us from Dr. Henry C. McGill although his colleague, Dr. Strong, has now been named as Principal Investigator. This is the study of the degree of atherosclerotic disease as determined at autopsy, principally of accident victims, for correlation with habits of life, principally smoking. Although the anniversary date is not until February 1, 1952, this renewal application has been submitted early to ascertain the intentions of the Board well in advance.

In renewing the grant at the December 1950 meeting, the Board promised only one year of support, and agreed that a conference should be held in an effort to clarify a number of questions that might bear upon our future plans.

These questions included:

(1) The accuracy with which atherosclerotic lesions can be graded.
(2) The reliability of information that can be obtained on the life habits of deceased people.
(3) Whether the lesions in other parts of the vascular system than the coronary arteries should be included in the study.
(4) Whether other research groups are engaged in similar work so that larger bodies of comparable data could be obtained by cooperation, and
(5) What kinds of conclusions should be possible if the data could be collected and the correlations made.

There may have been others.

The conference on atherosclerosis studies was held on May 26, 1951 with representatives from eight or nine different research groups present. Most of the members of the subcommittee attended.

I believe that Dr. McGill's feeling is that his methods for rating atherosclerotic lesions are satisfactory for his purposes and I think he feels that this also was the consensus of the group. He feels also, I think, that his pilot studies on determining smoking habits from close associates of living subjects, as verified by interrogating the subjects themselves, has justified his confidence in the data he can get on this subject from close associates of persons now deceased. He believes that he can do equally well in getting data on alcohol consumption and

he recognizes dietary information as equally or more important, he sees this as much more difficult and does not include it in his present plan, though the matter is under continuing study by his colleagues at the University of Louisiana.

With respect to other parts of the vascular system, he has a colleague who is interested particularly in the cerebral circulation and hopes to develop a collateral study of this system. This, however, is not included in his proposal to us, which is confined to study of the coronary arteries.

The conference did not reveal any other studies now underway with use of techniques sufficiently similar to suggest that any pooling of data would be possible.

The subcommittee must, therefore, reach a judgment as to whether the expenditure requested for the stated purposes will be a good investment or whether it can be made a good investment by expansion into a cooperative project or by other modification.

With respect to the kinds of conclusions that might be drawn from the work if it can be carried out successfully, there seem to be three possibilities:

(1) There may be a positive correlation between the degree of coronary arteriosclerosis and the amount of smoking.
(2) There may be a negative correlation, or
(3) There may be no correlation.

If there should be a positive correlation, the general situation would be much as it is already. That is, we would not really know whether the smoking caused the greater degree of disease by speeding up the process, or whether the association was indirect through other intermediate factors and not actually causal. Those who are eager to indict tobacco would undoubtedly seize upon any such result and employ it as another evidence that tobacco use is damaging to health, whether this conclusion was justified or not. Of course, if a sufficient number of other life habits could be studied simultaneously there would be a better chance of getting some real perspective.

If there should be a negative correlation, the degree of conclusiveness would be similar. We would not really be justified in concluding that tobacco use slows down the atherosclerotic process although this would be one possible hypothesis.

If there should be no correlation, the results would be more conclusive, since if the precision of the data were sufficient to make it certain that there was a real lack of correlation and not merely a methodological indeterminacy, we could then conclude that tobacco use actually does not accelerate atherosclerosis of the coronary arteries.

If my reasoning is correct, the study appears as a kind of gamble in which "heads we win but tails we do not lose for sure" (i.e., scientifically though we might in the newspaper headlines and even at the hands of "study groups").

Is there any basis for guessing what will be found? In a somewhat similar study, Spain found no correlation between smoking and the amount of disease in the coronary arteries.

At our conference, Thomas Dawber reported that the Framingham study found no correlation between smoking and the incidence of angina pectoris. They have done relatively little anatomic or pathological work. However, if one assumes that angina is a chronic manifestation of generalized atherosclerosis of the coronary arteries, the observation might suggest that probably no correlation would be found between smoking and the pathological condition found on autopsy. The Framingham group did find a positive correlation between smoking and myocardial infarction. The two observations can be reconciled by assuming that smoking might, directly or indirectly, contribute to the precipitation of an acute episode when the underlying conditions are conducive. This is a hypothetical concept, and I do not know of any mechanisms that have been elucidated or even proposed unless the reported but unsubstantiated effect of smoking on clotting time or hematocrit is considered to be such.

To determine whether smoking does or does not affect the rate of atherosclerosis by direct or indirect means would seem to be one of our most important mainstream problems. If we cannot get elucidation by study of human material, the chief alternative in sight is animal experiment. Our efforts along these lines with Dr. Wenzel were not very rewarding.

However, in a recent conference with Dr. Fredrick Stare, he expressed the opinion that animal experiments could be made meaningful. He thinks that dietary methods for producing atherosclerosis in animals are now sufficiently standardized and reproducible that studies could be designed to superimpose tobacco smoke inhalation upon a basic atherosclerotogenic regimen in half a dozen different species, including primates, and determine the effects of this added factor on the score.

The problem may be important enough to justify both human and animal studies. I plan to pursue discussions further with Stare and Ira Gore on the animal work.

Meanwhile we must determine how far we want to gamble on McGill's approach.

R.C.H.

RCH:ck